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Case Report

Refractory Hypoglycemia Secondary to the Warburg Effect in Diffuse Large B-Cell Lymphoma

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Abstract

Spontaneous and refractory hypoglycemia in malignancy poses diagnostic challenges, since its exact underlying mechanisms remain unclear. A 62-year-old female patient with a 10-year type 2 diabetes mellitus history presented with abdominal pain and spontaneous hypoglycemia despite discontinuation of her diabetic treatments. An initial computed tomography (CT) scan revealed a large perinephric tumor, and a second CT, performed a week later, demonstrated significant tumor growth. On admission, she had no neuroglycopenic symptoms despite a serum glucose level of 25 mg/dL (1.39 mmol/L). She showed suppressed insulin and insulin-like growth factor (IGF)-1 levels, elevated lactate levels, a pH of 7.434 with an anion gap of 24.1, and a negative test for anti-insulin antibody. A percutaneous CT-guided tumor biopsy revealed diffuse large B-cell lymphoma. She received continuous dextrose supplementation and prednisolone to alleviate the severe hypoglycemia, but she died from the tumor burden on the sixth day of hospitalization. Postmortem serum immunoblotting revealed the absence of partially processed IGF-2 precursors. The patient's refractory hypoglycemia and hyperlactatemia were consistent with tumor-associated aerobic glycolytic lactate production, known as the Warburg effect. This case illustrates the importance of increased awareness of this underrecognized oncologic emergency in the differential diagnosis of profound spontaneous hypoglycemia in malignancy.

Key Words: hypoglycemia, Warburg effect, hyperlactatemia, non-islet tumor-induced hypoglycemia, insulin-like growth factor 2, diffuse large B-cell lymphoma

Abbreviations: CT, computed tomography; DLBCL, diffuse large B-cell lymphoma; IGF, insulin-like growth factor; NICTH, non-islet tumor-induced hypoglycemia.

Introduction

Refractory hypoglycemia in patients with malignancies is an indicator of poor prognosis and usually requires early diagnosis of the underlying condition. However, identifying the cause of hypoglycemia is often a major challenge. Hepatic or adrenal insufficiency caused by extensive tumor invasion can lead to spontaneous hypoglycemia. Non-islet-cell tumor hypoglycemia (NICTH) is a rare, life-threatening paraneoplastic syndrome in which tumors secrete substances that interfere with glucose metabolism, most commonly due to a partially processed precursor of insulin-like growth factor (IGF)-2, called *big IGF-2* [1-3], and, very rarely, insulin [4], IGF-1 [5], or IGF-2 [6]. Far less frequently reported hypoglycemia due to the Warburg effect, an emergency condition with very poor outcomes, has been documented to be associated with lactic acidosis [7]. Lactic acidosis can occur in malignancies, especially lymphoproliferative disorders such as lymphomas [7-9]. When cancer cell metabolism shifts from oxidative phosphorylation to glycolysis under aerobic conditions, excess glucose is consumed, and large amounts of lactic acid are produced [10]. The diagnostic criteria for hypoglycemia due to the Warburg effect remain unclear, given the paucity of case reports and difficulty in differentiating it from NICTH. This article describes a case of diffuse large B-cell lymphoma (DLBCL) associated with profound hypoglycemia and hyperlactatemia, in which lactic acidosis was compensated by respiratory alkalosis and the presence of big IGF-2 was ruled out through serum immunoblotting.

Case Presentation

A 62-year-old Japanese female patient, who had been diagnosed with type 2 diabetes mellitus 10 years prior and was on a stable treatment regimen of metformin, dapagliflozin, and insulin glargine (12 units), noticed that her morning fingerstick glucose readings had dropped to below 70 mg/dL and reduced her insulin self-injection dosage. Within a week thereafter, she developed a fever and right lower abdominal pain and visited our outpatient clinic. Her laboratory findings were as follows: white blood cell count, 9800/μL (reference range: 3300-8600/μL); C-reactive protein, 2.73 mg/dL (27.3 mg/L, reference range: <0.14 mg/dL; <1.4 mg/L); blood glucose, 70 mg/dL (3.89 mmol/L, reference range: 60-110 mg/dL; 3.33-6.11 nmol/L); lactic dehydrogenase, 2609 U/L (reference

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range: 124-222 U/L); creatinine, 0.93 mg/dL (82.2 µmol/L, reference range: 0.46-0.79 mg/dL; 40.7-69.9 µmol/L); and urinary leukocytosis. Moreover, abdominal computed tomography (CT) revealed pyelonephritis, and a large perirenal tumor. She received oral levofloxacin (500 mg daily) without symptom relief. Several days later, she discontinued all her medications because her fingerstick glucose level decreased to 35 mg/dL (1.94 mmol/L). Re-examination after 1 week revealed spontaneous hypoglycemia (25 mg/dL [1.39 mmol/L]) and impaired renal function (serum creatinine, 1.42 mg/dL [125.5 µmol/L]; blood urea nitrogen, 31.1 mg/dL [11.1 mmol/L], reference range: 8-20 mg/dL [2.9-7.1 mmol/L]); accordingly, she was urgently hospitalized.

Upon admission, she had a height of 165.0 cm and a weight of 85.4 kg. She had a blood pressure of 117/65 mmHg, a pulse rate of 114 beats/min, a clear consciousness level with no cognitive, behavioral, or psychomotor impairment, a body temperature of 37.4 °C, and an oxygen saturation of 100% on room air. The only remarkable finding upon physical examination was tenderness in the right lower quadrant of her abdomen. The findings of the endocrine tests when her blood sugar level was 32 mg/dL (1.78 mmol/L) were as follows: immunoreactive insulin, 1.0 µU/mL (7.2 pmol/L) (reference range: 5-25 µU/mL [35.9-179.4 pmol/L]); C-peptide, 0.89 ng/mL (0.29 nmol/L) (reference range: 0.61-2.09 ng/mL [0.2-0.69 nmol/L]); growth hormone, 0.68 ng/mL (0.68 µg/L) (reference range: 5-25 ng/mL [5-25 µg/L]); IGF-1, 21 ng/mL (2.7 nmol/L) (age-adjusted normal: 68-196 µg/L, [8.9-25.6 nmol/L]); cortisol, 19.8 µg/dL (546.3 nmol/L) (reference range: 4.0-18.3 µg/dL [110.4-504.9 nmol/L]); adrenocorticotropic hormone, 33.9 pg/mL (7.46 pmol/L) (reference range: 6.6-63.2 pg/mL [1.5-13.9 pmol/L]); anti-insulin antibody lower than the detectable limit of 0.4 U/mL; soluble interleukin 2 receptor, 4410 U/mL (reference range: 157-474 U/mL); and CA125, 326.8 U/mL (reference range: <35 U/mL). No hemolysis was observed in any of the above plasma or serum samples. Arterial blood gas analysis revealed respiratory alkalosis and lactic acidosis as follows: pH, 7.434; pCO_2, 24.8 mmHg; pO_2, 93 mmHg; HCO_3^-, 16.6 mEq/L; extracellular base excess, −8 mmol/L; lactate, 46.6 mg/dL (5.2 mmol/L) (reference range: 3-17 mg/dL [0.33-1.89 mmol/L]); and a high anion gap of 24.1. Subsequent plain thoracic and abdominal CT revealed significant enlargement of the perinephric tumor within the week (Fig. 1).

Her serum creatinine level on the second hospitalization day was further elevated to 1.98 mg/dL (175.1 µmol/L). Magnetic resonance imaging revealed a large irregular tumor surrounding both kidneys, extending into the retroperitoneum of the pelvis and encroaching on the female genitalia and muscles. Placement of a right ureteral stent relieved the obstruction, and urine cytology obtained from the right renal pelvis revealed class V positivity for malignant cells. CT-guided biopsy was performed under general anesthesia and suggested malignant lymphoma. Her lactate dehydrogenase level markedly increased, reaching 12 133 U/L on the fifth hospitalization day. She developed massive intestinal bleeding and died on the sixth day after admission. No obvious neurologic symptoms due to the hypoglycemia were observed during hospitalization.

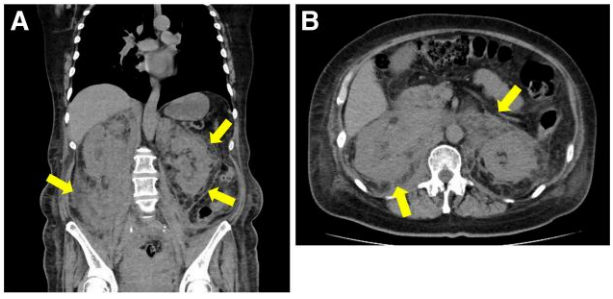

Figure 1. Computed tomographic scan at the first outpatient visit. Coronal (A) and axial (B) planes of the abdomen showing bilateral perirenal tumors (arrows).

Diagnostic Assessment

Postmortem histological examination of the tumor biopsy specimen revealed DLBCL with a Ki-67 index of 99% (Fig. 2). Her rapidly growing DLBCL was associated with marked hyperlactatemia and progressive profound spontaneous hypoglycemia without any signs/evidence of hepatic failure or adrenocortical insufficiency. Given that hypoglycemia caused by levofloxacin, which she received for several days, is very rare [11] and that her hypoglycemia became profound and refractory after cessation of all medications, drug-induced hypoglycemia was unlikely. Immunohistochemical staining of the tumor indicated limited IGF-2 expression, whereas serum immunoblotting was negative for large-molecular-weight IGF-2 (big IGF-2) (Fig. 3), and her serum IGF-2 level was 0.722 µg/mL (reference value, 0.390-0.799 µg/mL). These results rule out IGF-2/big IGF-2 as a cause of spontaneous progressive hypoglycemia. The adequately suppressed insulin and normal C-peptide levels at a blood glucose level of 32 mg/dL (1.78 mmol/L) excluded endogenous hyperinsulinism. We interpreted this type B lactic acidosis to be the result of excessive aerobic glycolysis due to the Warburg effect.

Treatment

On the admission day, intravenous dextrose infusion, 1.0 mg/kg/min, was required to raise her blood glucose level from 25 mg/dL (1.39 mmol/L) to >50 mg/dL (>2.78 mmol/L). The amount of daily dextrose required to maintain the blood sugar level at >50 mg/dL (>2.78 mmol/L) ultimately increased to 2.5 mg/kg/min over the course of the third day. Administration of 80 mg of prednisolone (1 mg/kg) partially reduced the intravenous dextrose requirement to 1.4 mg/kg/min. Chemotherapy against DLBCL could not be initiated.

Outcome and Follow-Up

Because the tumor was highly aggressive, the patient succumbed to the rapidly growing tumor burden before the histopathological diagnosis was established.

Discussion

In noncancer cells under aerobic conditions, glucose is converted to pyruvate for subsequent oxidative phosphorylation to generate ATP. In anaerobic cells that cannot produce adequate energy through oxidative phosphorylation, pyruvate transformed from glucose is converted into lactate by lactate dehydrogenase. Conversely, cancer cells may have altered metabolic features to promote growth and survival, characterized by an increased glucose uptake and accelerated conversion of glucose to lactate even in the presence of completely functioning mitochondria [12]. This metabolic phenotype in

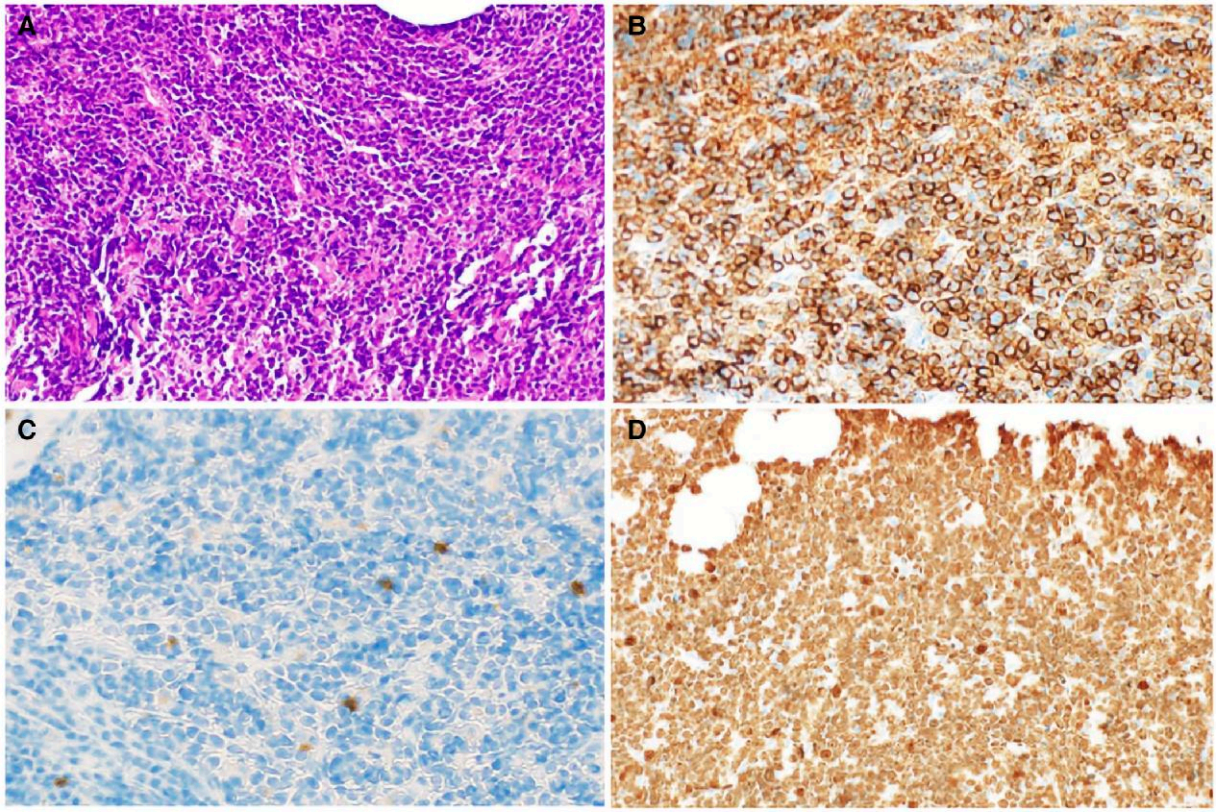

Figure 2. Microscopic findings of the resected specimens. (A) Hematoxylin and eosin staining in a high-power (400×) view showing diffuse proliferation of the abnormally large cells with nuclear swelling and concentration of the nuclear chromatin. (B-D) Immunohistochemistry showing that the abnormally large cells are positive for CD20 (B) and negative for CD3 (C), and the estimated Ki-67 labeling index is 99% (D).

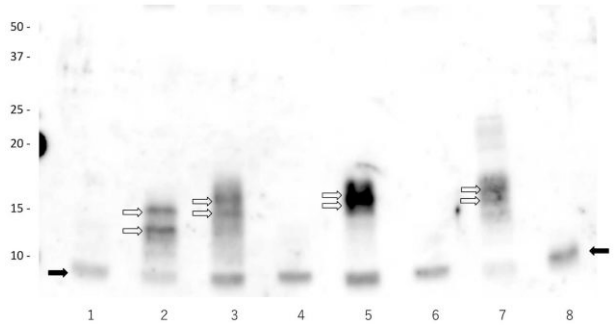

Figure 3. Distinct molecular forms of serum IGF-2 between the current patient and those with NICTH were identified by immunoblot analysis using the specific antibody. Serum samples (1 μL) were obtained from a healthy control (lane 1), the present patient (lane 4), and patients with NICTH before (lanes 2, 3, 5) and after surgical tumor resection (lane 6). Resected tumor extracts (5 μL protein) (lane 7) and recombinant human IGF-2 protein (MW 7 500, lane 8) were separated by 15% SDS-polyacrylamide gel electrophoresis and immunoblotted against anti-IGF-2 monoclonal antibody (1:3000: clone S1F2 Merck Millipore) and visualized by anti-mouse IgG-HRP (1:3000: #7076 Cell Signaling Technology). The open arrows denote the positions of unprocessed IGF-2 precursors, and the black arrow denotes authentic IGF-2 protein. The electrophoretic mobility is indicated for molecular weight standards covering 10 to 50 kDa.

aerobic glycolysis is known as the Warburg effect [10] and is more commonly documented in hematologic malignancies than in solid tumors [13]. Increased glycolysis due to the Warburg effect explains the coexistence of hypoglycemia and hyperlactatemia. Its association with profound spontaneous hypoglycemia without neuroglycopenic symptoms has recently attracted attention [14-19].

Lactate, previously regarded as a metabolic waste product, has been identified as an important energy source, substituting glucose as the brain's metabolic fuel [20-22]. Patients with severe Warburg hypoglycemia without neuroglycopenic symptoms have reduced fluorodeoxyglucose uptake in the brain [16, 17]. Thus, in our patient, the excess lactate produced could have prevented neuroglycopenic symptoms. Lactate is also known to induce histone lactylation, and this epigenetic modification exerts a potent promoting effect on gene transcription [23-25]. Accordingly, massive lactate accumulation is considered to be caused by an important tumor phenotype, potentially leading to an extremely poor prognosis [7, 8]. Aggressive glucose infusions in these patients would increase serum lactate levels [16], which may preferentially "feed" the tumor and exacerbate lactic acidosis. The only intervention reported to improve survival is early initiation of effective chemotherapy, which requires prompt diagnosis [7, 8, 13, 17, 26]. Although the use of steroids has been shown to reduce the requirement for intravenous dextrose, as in our case [15-17], further studies are needed to establish the management of metabolic control in patients with asymptomatic Warburg effect hypoglycemia.

The diagnostic criteria for hypoglycemia due to the Warburg effect remain unclear. Spontaneous profound hypoglycemia and lactic acidosis unexplained by other etiologies in patients with aggressive tumors who have poor prognoses have been ascribed to this diagnosis. Some recent reports

claim that a pH <7.35 is a diagnostic basis of Warburg effect hypoglycemia [14, 26]; however, acidemia does not always occur in lactic acidosis, given that coexisting acid-base disorders can increase the blood pH [27]. In our patient, arterial blood gas analysis revealed compensated respiratory alkalosis with hyperventilation-induced hypocapnia, which is a known feature of lactic acidosis, resulting in the absence of acidemia despite marked hyperlactatemia. Previous case reports on hypoglycemia due to the Warburg effect did not rule out NICTH as a causative mechanism for spontaneous hypoglycemia [8, 13-15, 18, 19, 26]. Conversely, case reports on NICTH did not rule out hypoglycemia due to the Warburg effect [1, 6, 28]. Progressive cancers and hematologic malignancies that produce big IGF-2 molecules may still simultaneously present with the Warburg effect. Patients with big IGF-2 present with low levels of serum immunoreactive insulin and C-peptide during hypoglycemia [29, 30]. However, a study comparing patients with spontaneous profound hypoglycemia with and without serum big IGF-2 molecules found that neither serum immunoreactive insulin/C-peptide levels nor serum IGF-1 levels could help distinguish NICTH from other causes of hypoglycemia in malignancies [28]. Therefore, the differential diagnosis of hypoglycemia due to the Warburg effect and NICTH requires information regarding lactic acidosis and big IGF-2 rather than other serum glucose-regulating hormone levels.

In conclusion, we report a patient with aggressive DLBCL who developed spontaneous profound asymptomatic hypoglycemia and lactic acidosis due to the Warburg effect. NICTH was ruled out by examining immunoreactive big IGF-2 levels and other substances interfering with glucose metabolism. Because hyperlactatemia occurring concomitantly with the Warburg effect prevents the neuroglycopenic symptoms of hypoglycemia and, at the same time, potently promotes tumor progression, clinicians should be well aware of this oncological emergency that warrants prompt diagnosis and aggressive treatment.

Learning Points

- Our patient had aggressively progressive DLBCL associated with profound hypoglycemia due to the Warburg effect.
- The differential diagnosis of spontaneous progressive hypoglycemia in malignancy requires information regarding lactic acidosis and big IGF-2.
- Clinical findings of the Warburg effect hypoglycemia may often be overlooked in many cases.
- Accordingly, awareness of the Warburg effect should be increased among oncologists and endocrinologists.

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Contributors

Mi.S., T.W., and S.Y. clinically managed the patient. Mi.S. wrote the first draft of the manuscript and created figures. T.W. and T.Y. reviewed the manuscript and figures for intellectual content. T.W. and Ma.S. were involved in the manuscript submission. I.F. performed immunoblotting and measurement of IGF-2 of the patient's serum. Ma.S. supervised the clinical management/diagnostic protocols and wrote the manuscript. All authors reviewed and approved the final draft.

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Disclosures

None declared.

Informed Patient Consent for Publication

Signed informed consent could not be obtained from the patient or a proxy but has been approved by the treating institution.

Data Availability Statement

Data sharing is not applicable to this article as no data sets were generated or analyzed.

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